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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	27

DATE MAILED: 11/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/759,207	PECKER ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's amendment filed 5-27-03 (Paper No. 24) is acknowledged and has been entered.

2. The terminal disclaimer filed on 5/27/00 (Paper No. 25) disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of the full statutory term defined in 35 USC 154 to 156 and 173, as presently shortened by any terminal disclaimer of prior US Patent No. 6,177,545 has been reviewed and is accepted. The terminal disclaimer has been recorded.

The following objection and rejections are necessitated by Applicant's amendment filed 5-27-03.

3. The amendment filed 5-27-03 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the amendment to insert a complete paragraph before line 1 on page 20 of the instant specification with regard to a polypeptide having heparanase activity which shares at least 60%, 70%, 80% or 90% homology with SEQ ID NO: 2, and the disclosure of "Homology between the polypeptide and SEQ ID NO: 2 may be determined with the sequence analysis software...".

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendatory material not supported by the specification and claims as originally filed is as follows: an isolated antibody specifically binding or elicited by at least one epitope of a mammalian heparanase protein, said heparanase protein being at least 80% or at least 90% homologous to SEQ ID NO: 2.

6. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed antibody specifically binding to or elicited by at least one epitope of a mammalian heparanase protein, said heparanase protein being at least 80% or at least 90% homologous to SEQ ID NO: 2.

The instant claims encompass antibodies to proteins that are specific for or elicited by heparanases of undisclosed structure. The said antibodies can be specific for or elicited by any heparanase protein with at least 80% or 90% homology to SEQ ID NO: 2. There is insufficient disclosure in the specification for said antibodies.

The specification discloses that anti-heparanase antibodies can be produced against heparanases that have widely disparate amino acid sequences, for example those cited on page 12 at lines 13-16 of the instant application, i.e., mouse B16-10 heparanase, human platelet heparanase, heparanases produced by several human tumor cell lines and CHO cells.

In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. However, a generic statement such as antibodies specific for or elicited by heparanase protein with at least 80% or 90% homology to SEQ ID NO: 2, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by the property of being specific for or elicted by a protein with at least 80% or at least 90% homology to SEQ ID NO: 2 and having heparanase activity. It does not specifically define any of the compounds that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others, other than that they are specific for or elicited by heparanases that are at least 80% or at least 90% homologous to SEQ ID NO: 2. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. In addition, a definition by function and in the instant case by partial structure where the activity is not correlated with a specific structural feature, does not suffice to define the genus because it is only an indication of what the property the heparanase protein has, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06. It is only a definition of a useful result rather than a definition of

what achieves that result. Many such species may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

One of ordinary skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

Applicant's arguments in the amendment filed 5-27-03 have been fully considered, but are not persuasive.

It is noted in Applicant's amendment filed 5-27-03 beginning on page 2 and continuing on to page 6, that it is Applicant's position that the instant application describes specific examples of anti-heparanase antibodies against heparanases that have widely disparate amino acid sequences, for example those cited on page 12 at lines 13-16 of the instant application, i.e., mouse B16-10 heparanase, human platelet heparanase, heparanases produced by several human tumor cell lines and CHO cells, that the mouse heparanase protein is known to have less than 80% sequence homology to human heparanase as described in WO 0052178. It is Applicant's further position that Appendix A of the said amendment shows homology and differences between human, rat , mouse and chicken heparanase sequences, that the heparanase binding site is marked. It is also Applicant's position that 08/922170 parent discloses that the recombinant heparanase taught includes those having 90% or 80% homology to SEQ ID NO: 2 of the instant application (SEQ ID NO: 10 of the said parent application), and that the claims do not need the wording to be literally present in the specification. It is Applicant's further position that the revised Guidelines at footnote 42 state that "examples of identifying characteristics include sequence, structure, binding affinity, binding specificity, molecular weight and length..." and that Applicant's disclosure is clearly sufficient to support a nexus between structure and function because the structure of the antibody is defined in terms of the protein it must recognize, which in turn has a structural limitation of being at least 90% homologous or at least 90% homologous to the specific taught heparanase sequence, and the protein is taught in terms of its function.

It is the Examiner's position that WO 0052178 is not part of the disclosure of the instant application, that none of the parent applications including 08/922170 have been incorporated by reference in the instant application, that in the sequences in Appendix A for several heparanases, the heparinase binding sites are not in the same position in the proteins and the said binding sites are not the same sequences, and in fact, the degree of homology of each is not stated in the said Appendix or amendment. One example of a mouse heparanase which is

less than 80% homologous with human heparanase is not adequate description of the claimed genus.

7. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention.

The specification does not disclose how make and or/use claimed antibody specifically binding to or elicited by at least one epitope of a mammalian heparanase protein, said heparanase protein being at least 80% or at least 90% homologous to SEQ ID NO: 2. The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass antibodies to proteins that are specific for or elicited by heparanases of undisclosed structure. The said antibodies can be specific for or elicited by any heparanase protein with at least 80% or 90% homology to SEQ ID NO: 2 which is 543 amino acid residues in length. There is insufficient disclosure in the specification for said antibodies.

The specification discloses that anti-heparanase antibodies can be produced against heparanases that have widely disparate amino acid sequences, for example those cited on page 12 at lines 13-16 of the instant application, i.e., mouse B16-10 heparanase, human platelet heparanase, heparanases produced by several human tumor cell lines and CHO cells.

There is no disclosure in the instant specification as to which amino acid residues at which positions comprise heparanase binding sites, which amino acid residues at other positions are tolerant of allowing the heparanase binding sites to function. Applicant presents examples in Appendix A of the said amendment in Appendix A for several heparanases of different sequence and the heparinase binding sites are not in the same position in the proteins and the said binding sites are not the same sequences.

The predictability of which changes can be tolerated in a polypeptide's amino acid sequence sand still retain function and properties requires a knowledge of, and guidance with regard to which amino acid residues at which positions in the amino acid sequence, if any are tolerant to modification and which are intolerant to modification, and detailed knowledge of the ways in which the product's structure relates to its function. Evidentiary reference Zhou et al (PNAS USA 1998, 95: 2492-7), provided in the previous Office Action) teaches that a single amino acid substitution in the HFE causes profound changes in the regulation of iron homeostasis in humans. Therefore, the problem of predicting functional aspects of the polypeptide product from mere sequence data of polypeptides being "at least 80%" or "at least 90% homologous to SEQ ID NO: 2" and what changes can be tolerated is complex and well outside the realm of routine experimentation.

There is insufficient guidance in the specification as to how to make and/or use the instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

Applicant's arguments in the amendment filed 5-27-03 have been fully considered but are not persuasive.

It is Applicant's position that the instant specification discloses an assay for heparanase activity, that one of ordinary skill in the art could perform such an assay, that Zhou et al teaches a protein that is not related to the heparanase family of proteins, that Applicant has submitted alignment data for several heparanases that are dissimilar in Appendix A of the said amendment, that examples of antibodies that recognize human, mouse and hamster heparanases are disclosed in Figures 18-20, that mouse heparanase has less than 80% homology to human heparanase, that the activity of the protein is a structural limitation on the antibody itself, and that Applicant has amended the disclosure to incorporate teachings from the parent application 08/922,170 into the instant application.

It is the Examiner's position that although the specification discloses an assay for heparanase activity and one of ordinary skill in the art could perform such an assay, that the heparanases shown in Appendix A show proteins which are dissimilar to some degree that is not stated, that the heparanase binding sites shown in these proteins are not the same sequences and are not present at the same position in the proteins, i.e., that there is not disclosure of what structure correlates to function of a protein that is at least 80% or at least 90% homologous to SEQ ID NO: 2, a 543 amino acid residue protein. It is the Examiner's further position that the said amendment of the disclosure to incorporate teachings from the parent application 08/922,170 into the instant application is improper and constitutes new matter as discussed supra in this Office Action. Although the protein taught by Zhou et al is not a heparanase, the teaching none-the-less is that a single amino acid change can abrogate function.

8. No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 703-308-0061. The examiner can normally be reached on Monday and Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Chan, can be reached on (703) 308-3973. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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November 10, 2003

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